REMARKS

Applicants respectfully request that the Examiner acknowledge receipt of the Information Disclosure Statement filed on December 10, 2003, and indicate, by making appropriate notations, that the documents listed in the Statement were considered.

I. Status of the Claims

Claims 12-31 are pending in this application. Claim 29 has been amended to delete a repeated word. Claim 30 has been amended to delete the phrase "or preventing." Applicants have not introduced any new matter by the amendments. Further, the amendments do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner.

II. Rejections under § 112, First Paragraph

The Examiner rejected pending claims 29-31 under 35 U.S.C. § 112, first paragraph, asserting that the specification, while being enabling for the treatment of hypertension, does not reasonably provide enablement for a method of activating soluble guanylate cyclase (sGC) or a method of treating all of the disorders of claim 30 or a method of preventing the disorders of claim 30, generally. Office Action at 2.

A claim is enabling if one of ordinary skill in the art can practice the claimed invention without undue experimentation. M.P.E.P. § 2164.01. To assess whether the experimentation is "undue," one may consider the eight factors outlined in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988): (1) breadth of the claims; (2) nature of the invention; (3) state of the prior art; (4) level of one of ordinary skill; (5) level of predictability in the art; (6) amount of direction provided by the invention; (7) existence of working examples; and (8) quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Regarding claims 29 and 31, directed towards a method of activating soluble guanylate cyclase, Applicants would like to point out that the specification on page 4, lines 7-10, states that the claimed compounds bring about strong guanylate cyclase activation. Furthermore, pages 29-30 of the specification describe an example of an experimental protocol used for activation of sGC and provide results of the n-fold stimulation of the enzyme by various compounds disclosed in the specification. Therefore, given the level of detail in the specification, including the presence of a working example, Applicants submit that the Examiner has failed to establish that claims 29 and 31 are not enabled. Applicants thus respectfully request that the rejection of claims 29 and 31 under § 112, first paragraph, be withdrawn.

The Examiner further rejected claim 30, directed towards a method of treating or preventing specific disorders. According to the Examiner, the specification does not reasonably provide enablement for a method of treating those disorders, except for hypertension, or enablement for a method of preventing all the disorders listed in claim 30. Applicants amend claim 30 to delete the phrase "or preventing." With respect to enablement for a method of treating the enumerated disorders, Applicants respectfully traverse the rejection.

The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04. "A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must be taken as being in compliance with the enablement requirement** . . . **unless there is a reason to**

doubt the objective truth of the statements contained therein . . . ." *Id.* (emphasis added). As the Examiner has provided no reason to doubt the objective truth of the statements contained in the specification, including the working example at pages 29-30, lack of enablement has not been established. Applicants therefore request that the rejection be withdrawn. *Id.*

Moreover, Applicants would like to point out that during the prosecution of the parent application 09/856,069, now issued as U.S. Patent No. 6,627,628, the present Examiner expressly acknowledged that the specification was "being enabling for the treatment of the [same] claimed diseases." See July 5, 2002, Office Action in Serial No. 09/856,069, at page 2.

In the present Office Action, the Examiner cited several state of the art references in support of his rejection. Those same references, however, in fact provide support to Applicants' assertion that, in light of the state of the prior art, the specification reasonably provides enablement for a method of treating the disorders recited in claim 30 by using the claimed compounds. For example, Carvajal et al. (Journal of Cellular Physiology 2000) on page 416 states that "cGMP should be regarded as a cornerstone molecule involved in SM [smooth muscle] relaxation" and "[i]t is generally accepted that cGMP triggers relaxation of SM by activating an intracellular molecular cascade, which revolves around the activity of PKG" (page 413). Similarly, Yamashita et al. (Hypertension 2000) provides on page 97 that "[a]ctivated sGC converts guanosine triphosphate to the intracellular second messenger cGMP, which relaxes vascular smooth muscle cells."

The Examiner also cited Wolin et al. (Biokhimiya 1998) in making the non-enablement rejection. This reference states that the "best documented action [of

cGMP] is to provide vascular relaxation." This reference, however, discusses signaling mechanisms, including activation of sGC, mediated by **oxidants and nitric oxide**, and not by other compounds. Similarly, Adnot et al. (PubMed abstract cited by the Examiner) discusses **nitric oxide-mediated** vasodilatation. Applicants note that the compounds of the instant invention do not activate sGC via release of nitric oxide. Consequently, these references do not provide a reasonable basis to question the enablement for the instant invention and to satisfy the Examiner's burden in challenging enablement.

Applicants further point out that another reference cited by the Examiner, Koren et al. (2002), recites that the most common predisposing condition associated with the development of diastolic congestive heart failure is hypertension. Since the Examiner expressly acknowledged that the specification enables treatment of hypertension (Office Action page 2), it follows that the specification reasonably provides enablement for treating or preventing diastolic dysfunction, such as diastolic congestive heart failure.

The Examiner also cited a reference dealing with platelet activation, Ko et al. (Blood 1994). That reference states on page 4226 that cGMP is a powerful inhibitor of platelet activation. In addition, "[t]here is also evidence that . . . cGMP can suppress platelet activation in vivo, indicating that an antiplatelet action may supplement their effects on vascular smooth muscle in the treatment of cardiovascular diseases." *Id.* Therefore, Applicants respectfully submit that the specification provides enablement for a method of treating or preventing disorders of claim 30 that are caused by or associated with platelet activation.

Furthermore, Applicants maintain that the specification enables a method of treating or preventing erectile dysfunction by using the claimed compounds as sGC

stimulators. For example Ayajiki et al. (PubMed abstract cited by the Examiner) states that "increase in cGMP by activation of sGC dilates cavernous smooth muscle and then induces penile erection." Therefore, Applicants respectfully submit that the Examiner has failed to establish that one skilled in the art, armed with the knowledge present in the state of the prior art as outlined by the Examiner himself, would need to engage in undue experimentation to practice the claimed invention. For all the foregoing reasons, Applicants respectfully request that the rejection of claim 30 under 35 U.S.C. § 112, first paragraph, be withdrawn.

III. Rejection under § 112, Second Paragraph

The Examiner rejected claim 29 under 35 U.S.C. § 112, second paragraph, based on his contention that the claim is indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner pointed out that the term "comprising" was repeated in the claim. In addition, the Examiner asserted that the claim is confusing because it is not understood "to what subject" the effective amount of the compound is added. Applicants amended claim 29 to delete the repeated word and respectfully traverse the remaining rejection.

In order to meet the requirements of 35 U.S.C. § 112, second paragraph, the claim must define the patentable subject matter with a reasonable degree of clarity and particularity. *See* M.P.E.P. § 2173.02. If the scope of the invention sought to be patented can be determined from the language of the claim with reasonable degree of certainty, then a rejection under 35 U.S.C. § 112, second paragraph, is not appropriate. *In re Wiggins*, 488 F.2d 538, 179 U.S.P.Q. 421 (C.C.P.A. 1973).

Claim 29 now recites "a method of activating soluble guanylate cyclase comprising addition of an effective amount of at least one compound. . . ." Definiteness of claim language must be analyzed in light of, among other factors, the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art. *See* M.P.E.P. § 2173.02. Applicants respectfully submit that one reasonable interpretation of claim 29 by a person of ordinary skill in the art is to add an effective amount of at least one of the claimed compounds to a biochemical investigation in which activation of sGC is intended. Specification page 19. Furthermore, during the prosecution of the parent application, 09/856,069, now issued as U.S. Patent No. 6,627,628, the present Examiner allowed Patent claim 9, which is worded identically to claim 29 of the present application. Therefore, the subject matter of claim 29 can be determined from its language with a reasonable degree of certainty and the rejection under 35 U.S.C. § 112, second paragraph, should be withdrawn.

IV. Nonstatutory Double Patenting Rejection

Claims 12-31 were rejected under the judicially-created doctrine of obviousness-type double patenting over claims 1-11 of U.S. Patent No. 6,627,628 (the parent of the present application). Applicants respectfully traverse. In an effort to expedite prosecution, however, Applicants submit herewith a Terminal Disclaimer. Applicants respectfully request that these rejections be withdrawn.

V. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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